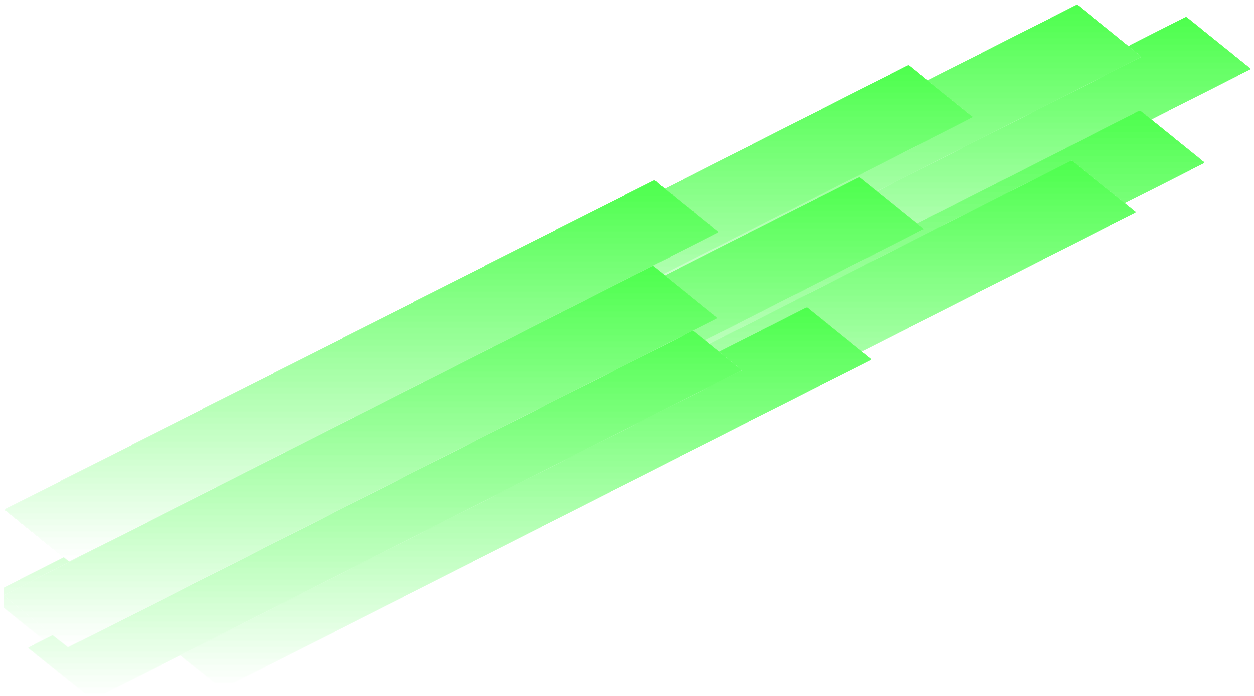
Guidance for Industry

Labeling Guidance for Butalbital, Acetaminophen, Caffeine and Hydrocodone Bitartrate Tablets



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
September 1997
OGD-L-6-R1

Guidance for Industry

Labeling Guidance for Butalbital, Acetaminophen, Caffeine and Hydrocodone Bitartrate Tablets

Additional copies are available from:

Office of Generic Drugs
Division of Labeling and Program Support
Labeling Review Branch
Attention: Team Leader
MetroPark North II
7500 Standish Place, Room 266N
Rockville, MD 20855-2773

(Tel) 301-827-5846
(Internet) http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
September 1997
OGD-L-6-R1

GUIDANCE FOR INDUSTRY[1]

Labeling Guidance for Butalbital, Acetaminophen, Caffeine and Hydrocodone Bitartrate Tablets

I. INTRODUCTION

This guidance describes the recommended labeling to comply with 21 CFR 314.94(a)(8)(iv) for an abbreviated new drug application. The basis of this guidance is the approved labeling of the reference listed drug (FIORICET WITH CODEINE®; Sandoz Pharmaceutical; 20-232/S-004; Approved January 18, 1996; Revised October 1994). Differences between the reference listed drug and this guidance may exist and may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, or omission of an indication or other aspects of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the Federal Food, Drug, and Cosmetic Act.

II. LABELING

CIII
[Include unless excepted status has been obtained from DEA.]

BUTALBITAL, ACETAMINOPHEN, CAFFEINE and HYDROCODONE BITARTRATE TABLETS

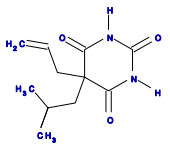
DESCRIPTION

Butalbital, acetaminophen, caffeine and hydrocodone bitartrate is supplied in tablet form for oral administration.

Butalbital (5-Allyl-5-isobutylbarbituric acid), a slightly bitter, white, odorless, crystalline powder, is a short to intermediate-acting barbiturate. It has the following structural formula:

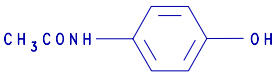
---

[1]This guidance has been prepared by the Office of Generic Drugs, Division of Labeling and Program Support in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on the development of labeling for an abbreviated new drug application. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirement of the applicable statute, regulations, or both.



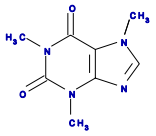
$C_{11}H_{16}N_2O_3$ MW = 224.26

Acetaminophen (4'-hydroxyacetanilide), a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:



$C_8H_9NO_2$ MW = 151.17

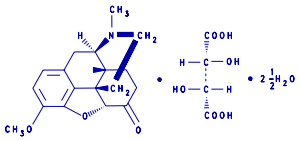
Caffeine (1,3,7-Trimethylxanthine), a bitter, white powder or white-glistening needles, is a central nervous system stimulant. It has the following structural formula:



$C_8H_{10}N_4O_2$

MW = 194.19

Hydrocodone bitartrate is an opioid analgesic and antitussive and occurs as fine, white crystals or as a crystalline powder. It is affected by light. The chemical name is 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:



$C_{18}H_{21}NO_3.C_4H_6O_6.2½H_2O$ MW = 494.50

Each tablet contains:

Hydrocodone Bitartrate, USP	___ mg
Warning: May be habit forming	
Butalbital, USP	___ mg
Warning: May be habit forming	
Acetaminophen, USP	___ mg
Caffeine, USP	___ mg

In addition each tablet contains the following inactive ingredients:

[Please note in accordance with good pharmaceutical practice, all dosage forms should be labeled to cite all the inactive ingredients (refer to USP General Chapter <1091> for guidance).]

CLINICAL PHARMACOLOGY

This combination drug product is intended as a treatment for tension headache.

It consists of a fixed combination of butalbital, acetaminophen, caffeine, and hydrocodone bitartrate. The role each component plays in the relief of the complex of symptoms known as tension headache is incompletely understood.

Pharmacokinetics: The behavior of the individual components is described below.

Hydrocodone: Hydrocodone is a semisynthetic narcotic analgesic and antitussive with multiple actions qualitatively similar to those of codeine. Most of these involve the central nervous system and smooth muscle. The precise mechanism of action of hydrocodone and other opiates is not known, although it is believed to relate to the existence of opiate receptors in the central nervous system. In addition to analgesia, narcotics may produce drowsiness, changes in mood and mental

clouding.

Following a 10 mg oral dose of hydrocodone administered to five adult male subjects, the mean peak concentration was 23.6 ± 5.2 ng/mL. Maximum serum levels were achieved at 1.3 ± 0.3 hours and the half-life was determined to be 3.8 ± 0.3 hours. Hydrocodone exhibits a complex pattern of metabolism including O-demethylation, N-demethylation and 6-keto reduction to the corresponding 6-α- and 6-ß-hydroxymetabolites.

See OVERDOSAGE for toxicity information.

Butalbital: Butalbital is well absorbed from the gastrointestinal tract and is expected to distribute to most tissues in the body. Barbiturates in general may appear in breast milk and readily cross the placental barrier. They are bound to plasma and tissue proteins to a varying degree and binding increases directly as a function of lipid solubility.

Elimination of butalbital is primarily via the kidney (59% to 88% of the dose) as unchanged drug or metabolites. The plasma half-life is about 35 hours. Urinary excretion products include parent drug (about 3.6% of the dose), 5-isobutyl-5-(2,3-dihydroxypropyl) barbituric acid (about 24% of the dose), 5-allyl-5(3-hydroxy-2-methyl-1-propyl) barbituric acid (about 4.8% of the dose), products with the barbituric acid ring hydrolyzed with excretion of urea (about 14% of the dose), as well as unidentified materials. Of the material excreted in the urine, 32% is conjugated.

The *in vitro* plasma protein binding of butalbital is 45% over the concentration range of 0.5 to 20 mcg/mL. This falls within the range of plasma protein binding (20% to 45%) reported with other barbiturates such as phenobarbital, pentobarbital, ans secobarbital sodium. The plasma-to-blood concentration ratio was almost unity indicating that there is no preferential distribution of butalbital into either plasma or blood cells. (See OVERDOSAGE for toxicity information.)

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug. (See OVERDOSAGE for toxicity information.)

Caffeine: Like most xanthines, caffeine is rapidly absorbed and distributed in all body tissues and fluids, including the CNS, fetal tissues, and breast milk.

Caffeine is cleared through metabolism and excretion in the urine. The plasma half-life is about 3 hours. Hepatic biotransformation prior to excretion, results in about equal amounts of 1-methyl-xanthine and 1-methyluric acid. Of the 70% of the dose that is recovered in the urine, only 3% is

unchanged drug. (See OVERDOSAGE for toxicity information.)

INDICATIONS AND USAGE

Butalbital, acetaminophen, caffeine, and hydrocodone bitartrate tablets are indicated for the relief of the symptom complex of tension (or muscle contraction) headache.

Evidence supporting the efficacy and safety of this combination product in the treatment of multiple recurrent headaches is unavailable. Caution in this regard is required because hydrocodone and butalbital are habit-forming and potentially abusable.

CONTRAINDICATIONS

This product is contraindicated under the following conditions:

- Hypersensitivity or intolerance to any component of this product.

- Patients with porphyria.

WARNINGS

In the presence of head injury or other intracranial lesions, the respiratory depressant effects of hydrocodone and other narcotics may be markedly enhanced, as well as their capacity for elevating cerebrospinal fluid pressure. Narcotics also produce other central nervous system (CNS) depressant effects, such as drowsiness, that may further obscure the clinical course of the patients with head injuries.

Hydrocodone or other narcotics may obscure signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions.

Butalbital and hydrocodone are habit-forming and potentially abusable. Consequently, the extended use of this product is not recommended.

PRECAUTIONS

General: Butalbital, acetaminophen, caffeine, and hydrocodone bitartrate tablets should be prescribed with caution in certain special-risk patients, such as the elderly or debilitated, and those with severe impairment of renal or hepatic function, head injuries, elevated intracranial pressure, acute abdominal conditions, hypothyroidism, urethral stricture, Addison's disease, or prostatic hypertrophy.

Information for Patients: This product may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking this product.

Alcohol and other CNS depressants may produce an additive CNS depression, when taken with this combination product, and should be avoided.

Hydrocodone and butalbital may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: The CNS effects of butalbital may be enhanced by monoamine oxidase (MAO) inhibitors. The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

Butalbital, acetaminophen, caffeine, and hydrocodone may enhance the effects of: other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants such as antihistamines, antipsychotics, or anti-anxiety agents, causing increased CNS depression.

Drug/Laboratory Test Interactions: Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether butalbital, acetaminophen, or hydrocodone have a potential for carcinogenesis, mutagenesis or impairment of fertility.

Pregnancy: Teratogenic Effects: *Pregnancy Category C*: Animal reproduction studies have not been conducted with this combination product. It is also not known whether butalbital, acetaminophen, caffeine, and hydrocodone bitartrate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. This product should be given to a

pregnant woman only when clearly needed.

Nonteratogenic Effects: Babies born to mothers who have been taking opioids regularly prior to delivery will be physically dependent. The withdrawal signs include irritability and excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting and fever. The intensity of the syndrome does not always correlate with the duration of maternal opioid use or dose. There is no consensus on the best method of managing withdrawal.

Withdrawal seizures were reported in a two-day-old male infant whose mother had taken a butalbital-containing drug during the last two months of pregnancy. Butalbital was found in the infant's serum. The infant was given phenobarbital 5 mg/kg, which was tapered without further seizure or other withdrawal symptoms.

Labor and Delivery: As with all narcotics, administration of this product to the mother shortly before delivery may result in some degree of respiratory depression in the newborn, especially if higher doses are used.

Nursing Mothers: Caffeine, barbiturates and acetaminophen are excreted in breast milk in small amounts, but the significance of their effects on nursing infants is not known. It is not known whether hydrocodone is excreted in human milk. Because of potential for serious adverse reactions in nursing infants from butalbital, acetaminophen, caffeine, and hydrocodone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 12 have not been established.

ADVERSE REACTIONS

Frequently Observed: The most frequently reported adverse reactions are drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, abdominal pain, and intoxicated feeling.

Infrequently Observed: All adverse events tabulated below are classified as infrequent.

Central Nervous: headache, shaky feeling, tingling, agitation, fainting, fatigue, heavy eyelids, high energy, hot spells, numbness, sluggishness, seizure, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, psychic dependence, and mood changes. Mental confusion, excitement or depression can also occur due to intolerance, particularly in elderly or debilitated patients, or due to overdosage of butalbital.

Autonomic Nervous: dry mouth, hyperhidrosis.

Gastrointestinal: difficulty swallowing, heartburn, flatulence, constipation.

Cardiovascular: tachycardia.

Musculoskeletal: leg pain, muscle fatigue.

Genitourinary: diuresis, ureteral spasm, spasm of vesical sphincters and urinary retention have been reported with opiates.

Respiratory Depression: Hydrocodone bitartrate may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVERDOSAGE).

Miscellaneous: pruritus, fever, earache, nasal congestion, tinnitus, euphoria, allergic reactions.

Several cases of dermatological reactions, including toxic epidermal necrolysis and erythema multiforme, have been reported
for a combination product containing butalbital, acetaminophen, and caffeine.

The following adverse drug events may be borne in mind as potential effects of the components of this product. Potential effects of high dosage are listed in the OVERDOSAGE section.

Acetaminophen: allergic reactions, rash, thrombocytopenia, agranulocytosis.

Caffeine: cardiac stimulation, irritability, tremor, dependence, nephrotoxicity, hyperglycemia.

Hydrocodone: nausea, vomiting, drowsiness, lightheadedness, constipation, pruritus, skin rash.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Butalbital, acetaminophen, caffeine, and hydrocodone bitartrate tablets are classified as a Schedule III controlled substance.

Abuse and Dependence: Hydrocodone: Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of narcotics; therefore, this product should be prescribed and administered with caution. However, psychic dependence is unlikely to develop when hydrocodone bitartrate is used for a short time.

Physical dependence, the condition in which continued administration of the drug is required to prevent the appearance of a withdrawal syndrome, assumes clinically significant proportions only after several weeks of continued narcotic use, although some mild degree of physical dependence

may develop after a few days of narcotic therapy. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is manifested initially by a shortened duration of analgesic effect, and subsequently by decreases in the intensity of analgesia. The rate of development of tolerance varies among patients.

Butalbital: Barbiturates may be habit-forming: Tolerance, psychological dependence, and physical dependence may occur especially following prolonged use of high doses of barbiturates. The average daily dose for the barbiturate addict is usually about 1500 mg. As tolerance to barbiturates develops, the amount needed to maintain the same level of intoxication increases; tolerance to a fatal dosage, however, does not increase more than two-fold. As this occurs, the margin between an intoxication dosage and fatal dosage becomes smaller. The lethal dose of a barbiturate is far less if alcohol is also ingested. Major withdrawal symptoms (convulsions and delirium) may occur within 16 hours and last up to 5 days after abrupt cessation of these drugs. Intensity of withdrawal symptoms gradually declines over a period of approximately 15 days. Treatment of barbiturate dependence consists of cautious and gradual withdrawal of the drug. Barbiturate-dependent patients can be withdrawn by using a number of different withdrawal regimens. One method involves initiating treatment at the patient's regular dosage level and gradually decreasing the daily dosage as tolerated by the patient.

OVERDOSAGE

Following an acute overdosage of butalbital, acetaminophen, caffeine, and hydrocodone, toxicity may result from the barbiturate, hydrocodone, or the acetaminophen components. Toxicity due to caffeine is less likely, due to the relatively small amounts in this formulation.

Signs and Symptoms: Toxicity from *barbiturate* poisoning includes drowsiness, confusion, and coma; respiratory depression; hypotension; and hypovolemic shock.

Serious overdose with *hydrocodone* is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis) extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

In *acetaminophen* overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necroses, hypoglycemic coma and thrombocytopenia may also occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion. In adults hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams, or fatalities with less than 15 grams.

Acute *caffeine* poisoning may cause insomnia, restlessness, tremor, and delirium, tachycardia and

extrasystoles.

Treatment: A single or multiple overdose with this combination product is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Pressors should be avoided. A cuffed endotracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration. If renal function is normal, forced diuresis may aid in the elimination of the barbiturate. Alkalinization of the urine increases renal excretion of some barbiturates, especially phenobarbital.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of hydrocodone may exceed that of the naloxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

If the dose of acetaminophen may have exceeded 140 mg/kg, acetyl-cysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24 hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

Toxic Doses (for adults):

Butalbital: toxic dose 1 g
(__ tablets)

Acetaminophen: toxic dose 10 g
(__ tablets)

Caffeine: toxic dose 1 g
(__ tablets)

DOSAGE AND ADMINISTRATION

One to two tablets every four hours. Total daily dosage should not exceed 6 tablets.

Extended and repeated use of this product is not recommended because of the potential for physical dependence.

HOW SUPPLIED

- Established Name
- Strength of dosage form
- Packaging, NDC number
- Dosage form, shape, color, scoring
- Store below 30°C (86°F).
- Dispense in a tight container, as defined in the USP.
- "Caution: Federal Law..." statement.

Include the following information at the end of the HOW SUPPLIED section:

- Date of latest revision.
- "Manufactured by" statement. - Should be consistent with container labels and/or carton labeling.

CONTAINER LABEL

In addition to the general label requirements ("Caution: Federal Law..." statement, statement of net quantity, etc.) please include the following:

Main Panel:

- To meet both the requirements for use of the established name and the need to easily

identify the intended product without undue repetition, we suggest the following:

Butalbital*	___ mg
Acetaminophen	___ mg
Caffeine	___ mg
and	
Hydrocodone* Bitartrate	___ mg
Tablets	

*Warning: May be habit forming.

Please note that the milligram amounts of each of the active ingredients would appear in a separate print type or colored boxes so as not to be a part of the established name, yet be positioned such that the drug component is easily identifiable to the appropriate strength.

If the above format is not possible we suggest the following:

Butalbital*, Acetaminophen, Caffeine and Hydrocodone* Bitartrate Tablets
___ mg/__ mg/__ mg and __ mg

*Warning: May be habit forming.

- The "Each tablet contains..." statement should read as follows:

Each tablet contains:

Butalbital, USP.....	__ mg
*Warning: May be habit forming	
Acetaminophen, USP.....	__ mg
Caffeine, USP.....	__ mg
Hydrocodone* Bitartrate, USP.....	__ mg

- Include the controlled substance symbol.